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10/606,162	06/25/2003	Jose Remacle	KLAUS2.002AUS	3585

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EXAMINER	
PETERSEN, CLARK D	
ART UNIT	**PAPER NUMBER**
1657	

NOTIFICATION DATE	DELIVERY MODE
08/10/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/606,162	REMACLE ET AL.	
	Examiner	Art Unit	
	Clark D. Petersen	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7-9 and 11-36* is/are pending in the application.

4a) Of the above claim(s) *16-21 and 30-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7-9,11-15 and 22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8 June 2007 has been entered.

This action is in response to the amendment, filed 8 June 2007, in which claims 1 and 22 were amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All objections and rejections not repeated in the instant Action have been withdrawn due to Applicant's response to the previous Action.

Status of the Claims

Claims 1, 4, 7-9 and 11-36 have been presented for examination. Claims 16-21 and 30-36 stand finally withdrawn from consideration and should have been canceled in response to the Final rejection of 08 Jan 2007.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 7-9, 11-15, and 22-29 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants now argue that cell activation can always be determined by analyzing any three proteins from Tables 1, 2, or 3; in the election of species requirement this list was narrowed to a combination of PAK6, CDK8, and MKK3. Applicants argue that any person who measures the phosphorylation state of any 3 proteins listed in instant Tables 1, 2 and 3 from a cell extract will be able to determine that a cell is activated. That is, two must have a change in phosphorylation while one must not: see Remarks at p. 10, referring to Appendix C, included as an affidavit in the documents submitted 8 June 2007. In previous Office Actions, Examiner has allowed Applicants wide latitude regarding the term "cell activation". However Applicants currently have defined "cell activation" as a state in which 2 out of 3 proteins that are randomly chosen for analysis show changes in phosphorylation; there is no other guidance for a common set of criteria for "cell activation". It must be so because three are required; showing any two are phosphorylated is not sufficient, as Applicants argue that the teachings of Paweletz et al, who also demonstrate the enhanced phosphorylation of two proteins in a disease state, are not anticipatory of demonstrating "cell activation". Given that the definition has changed,

Applicants must explain what cell activity is being enhanced by phosphorylation of any two of the proteins from Tables 1, 2 and 3. Additionally the examples provided in the instant Specification contradict the notion that 2 out of any 3 proteins must be phosphorylated; Example 5, submitted as a demonstration of determination of cell activation, states that 5 proteins were analyzed for their phosphorylation state, but only one (Erk1/2) demonstrates an increase in response to PMA application. Therefore the instant application is not enabled for the determination of cell activation by measurement of phosphorylation state of 3 proteins.

Claims 1 and 15 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

This rejection was previously presented in the Office Action mailed 8 January 2007 and is maintained for reasons of record and as set forth below.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claim 15 is drawn to a method of evaluating cell activation by evaluating the phosphorylation state of specific, named proteins from the list of Table I in the specification. Further, the claim is restricted according to the restriction requirement sent March

27, 2006 and the responsive election filed May 2, 2006, to the determination of cell activation by measuring phosphorylation of CDK8, PAK6, and MKK3.

Breadth of the claims: The claims are narrow in that applicant proposes to measure an aspect of cell activation by studying three cellular proteins in particular, namely CDK8, PAK6, and MKK3.

Guidance of the specification and existence of working examples: The specification provides guidance generally in determining the level of phosphorylation of a protein, or a cascade of proteins, in a comparison of activated versus untreated cells. Specific examples are given in the working examples of experiments performed with Akt, Erk, p38, as a few examples. However no working examples are given for determining phosphorylation status of CDK8, MKK3, or PAK6, and mention of these kinases is absent elsewhere in the specification, other than in Table 1 which provides guidance for the claims.

Predictability and state of the art: Studying phosphorylation of cellular proteins is a well-accepted method of studying aspects of cell physiology. It is reasonable to characterize the phosphorylation of members of signaling cascades along with changes in cellular dynamics. However CDK8 is unique among CDKs in that it appears that its activation is not dependent on phosphorylation as is observed with other CDK family members. Hoeppner et al (2005) determined that CDK8 is lacking the threonine in its activation loop that is present in other CDKs, and is phosphorylated to activate such CDKs. Rather CDK8 is activated by interaction of the residue that replaces the otherwise-phosphorylated threonine with its binding partner Cyclin C (see Possible mechanisms of CDK8 Activation, pp. 839-840, for example).

Therefore, no evidence is provided in either the instant specification for determination of activation of CDK8 by phosphorylation, and there is evidence in the literature that phosphorylation of CDK8 is not an effective means of determining cellular activation state.

Amount of experimentation necessary: As discussed above, the instant specification describes generally a method of characterizing cellular physiological responses to activating stimuli by measuring phosphorylation of components of cellular signaling cascades. It provides working examples for measuring phosphorylation of members of a few pathways including Akt, ERK, and p38, among others. However the instant specification does not provide working examples of phospho-specific antibodies for the elected species CDK8 and PAK6 and it is therefore not detailed enough to allow one of ordinary skill in the art to perform a cell activation assay using phosphorylation of these signaling molecules as a readout.

In view of the lack of guidance from the specification, the absence of working examples, literature that undermines the assertions of the instant application, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore claims 1 and 15, as they are drawn to the elected species of the combination of CDK8, PAK6, and MKK3, are not considered to be enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 7-9, 11-15, and 22-29 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "cell activation" is indefinite. It is unclear from the examples cited what "cell activation" is, and there is no clear definition in the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 7-9, 11, 12, 14, 22-27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schooler et al (Anal Biochem, 2000) in view of Paweletz et al (Oncogene, 2001).

This rejection was previously presented in the Office Action mailed 8 January 2007 and is maintained for reasons of record and as set forth below.

Schooler et al teach a ratiometric assay of epidermal growth factor receptor tyrosine kinase activation. They teach the measurement of EGFR activation in the MDA-MB-468 cell line (see p. 136, col. 2, for example). They teach that they treat the cells with purified epidermal growth factor, reading on 26 and 27 (see p. 136, col. 2, for example). They teach that 96 well plates, which fit the definition of plastic solid supports, are coated with anti-EGFR antibody, a capture molecule. Cell lysates - treated or untreated with EGFR – are added to the wells and incubated so the antibody captures EGFR in the lysates. The plates are washed, and phosphotyrosine antibody is added to half the wells while general EGFR antibody, which detects EGFR regardless of phosphorylation state, is added to the other half of the wells on each plate

(see "Tyr(P)/EGFR ELISA", pp. 136-137, for example). By this method they can determine the ratio of phosphorylated to total EGFR in response to treatment with EGF. They teach that their assay is a rapid, sensitive, and reliable means to assess receptor tyrosine kinase activity in all cell types (see p. 141, col. 2, for example).

Additionally Schooler teaches a method of detecting phosphorylation of the EGFR in response to EGF administration, reading on a chemical treatment as recited in claim 27.

Schooler et al do not expressly teach that first and second arrays are present on different supports, and that different populations of cells are assayed and compared.

Schooler et al do not teach that three different proteins should be simultaneously assayed for their phosphorylation state in a method of determining cell activation.

Paweletz et al teach a method of microdissecting distinct cell populations, from within and from around a tumor, from a single patient. They collect cellular lysates and immobilize them on slides made of nitrocellulose and glass. They analyze the phosphorylation state of Akt and ERK, for example, and correlate it with tumor progression, which reads on evaluating an activated state of cells (see Results, p. 1985, Fig. 5, p. 1986, and Materials and Methods pp. 1987-1988, for example). Paweletz et al also teach that multiple slides can be employed in their method, some slides treated as negative controls while separate slides are treated as experimental slides (see p. 1982, col. 2, for example). It is known in the art that cancer derives from accumulated genetic mutations, reading on claim 24. Because cancer is a disease in which cells dedifferentiate to some degree, the teachings of Paweletz et al read on claim 25.

A person of ordinary skill in the art at the time the invention was made would have been motivated to capture phosphorylated proteins in an array by specific epitope binding capture

molecules immobilized on the array, because Paweletz et al teach that observing the phosphorylation state of multiple proteins in parallel yields a signature of diseased tissue, and Schooler et al teach that one can observe proteins on a solid support in a sensitive, reliable way by capturing phosphorylated proteins on a solid support with immobilized epitope-binding capture molecules and then using phosphospecific antibodies to detect phosphorylation status, and that this method should be amenable to many different signaling molecules.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to immobilize multiple proteins on a solid support array through the use of epitope-binding capture molecules followed by detection of total versus phosphorylated proteins.

Claims 1, 4, 7-9, 11-15, 22-27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schooler et al (Anal Biochem, 2000) in view of Paweletz et al (Oncogene, 2001) and in view of Lee et al (2001).

This rejection was previously presented in the Office Action mailed 8 January 2007 and is maintained for reasons of record and as set forth below.

The teachings of Schooler et al are discussed above and applied as before.

The teachings of Paweletz et al are discussed above and applied as before.

Paweletz et al and Schooler et al do not expressly teach study of phosphorylation status of a transcription factor or MKK3.

Lee et al teach that it is possible to activate cells with a chemical treatment, in this case a transfection mixture comprising a transfectable plasmid for β-pix, which leads to

phosphorylation of MKK3 and the transcription factor ATF-2. They demonstrate that they can determine the ratio of phosphorylated MKK3 and ATF-2 to unphosphorylated MKK3 and ATF-2 with an antibodies specific to phospho-MKK3 and phospho-ATF2, and use it measure activation of these proteins in cells activated with the β-Pix transfection mixture vs. untreated cells (see Materials and Methods, pp.25067-25068, and see Fig. 5, p. 25069, as examples).

A person of ordinary skill in the art at the time the invention was made would have been motivated to measure phosphorylation of a transcription factor in a method of measuring cell activation, because Lee et al teach that transcription factors such as ATF2 are targets of kinases such as p38 which respond to activating signals such as growth factors (see Fig. 3, p. 25068, for example), and that MKK3 also responds to stimuli which mimic activating growth factors (see Fig. 5, p. 25069, for example).

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to study the phosphorylation status of a transcription factor, as well as MKK3, in a method of studying cell activation.

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schooler et al in view of Paweletz et al, and further in view of Gustafson et al (US Patent # 5413939, issued 5/9/1995).

This rejection was previously presented in the Office Action mailed 8 January 2007 and is maintained for reasons of record and as set forth below.

The teachings of Schooler et al are discussed above and applied as before.

The teachings of Paweletz et al are discussed above and applied as before.

Paweletz et al and Schooler et al do not expressly teach that metals, compact discs and electronic devices can be used in a method of testing cell activation.

Gustafson et al describe a method of binding antigens or antibodies to a compact disc, adding the complementary antigen or antibody, and then testing interferometrically the binding of antigen to antibody. Gustafson et al also teach that metals can be used for immobilizing protein with the expectation of measuring binding properties of complementary molecules (see col. 1, lines 29-36).

A person of ordinary skill in the art at the time the invention was made would have been motivated to use a metal surface, or a compact disc, and do measurements electronically in a method of determining cell activation by measuring binding of phosphospecific antibodies to immobilized phosphoproteins, because Gustafson et al teach that one can bind proteins to a metal surface or compact disc, and then efficiently test binding of antibodies to the immobilized proteins, in the instant situation using the technique of interferometry. One would have been motivated to do so, because Gustafson et al teach that their system is characterized by high linearity, a large dynamic range, a background free output, few process steps, short incubation times, and low coefficient of variation in relation to a standard measurement (see col. 2, lines 10-29, for example). Gustafson et al also teach that immobilizing proteins on metal surfaces allows light to reflect, making possible detection of changes in wavelength of that reflected light which can be correlated with binding of an analyte, such as an antibody.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to was made to use a metal surface, or a compact disc, and do

measurements electronically in a method of determining cell activation by measuring binding of phosphospecific antibodies to immobilized phosphoproteins.

Claims 1, 4, 7-9, 11, 12, 14, 22-27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schooler et al in view of Paweletz et al and further in view of Chang et al (USPGPub US2002/0192654 A1, filed 6/15/2001).

This rejection was previously presented in the Office Action mailed 8 January 2007 and is maintained for reasons of record and as set forth below.

The teachings of Schooler et al are discussed above and applied as before.

The teachings of Paweletz et al are discussed above and applied as before.

Paweletz et al and Schooler et al do not expressly teach the use of silicon as a solid support for phosphoproteins in a method of determining cell activation.

Chang et al teach that it is well known in the art to use silicon as a bio-chip substrate for DNA or protein immobilization (see Page 1, paragraph 0002, for example). They teach that the concept of the biochip was developed in the late twentieth century, and that the biochip is broadly defined as a product for immobilizing DNA, protein, or cell structures on a silicon for biochemical analysis.

A person of ordinary skill in the art at the time the invention was made would have been motivated to use a silicon support in a method of measuring phosphoproteins for the purpose of determining cell activation, because determining cell activation depends on immobilizing phosphoproteins on a solid support, and Chang et al teach that silicon is useful as a support for immobilized proteins because it is a material associated with high reliability, and rapid and accurate analysis (see para [0002], for example).

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to immobilize capture molecules on silicon supports in a method of studying cell activation.

Claims 22 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schooler et al in view of Paweletz et al and in view of Matsui et al (EMBO J, 1996).

This rejection was previously presented in the Office Action mailed 8 January 2007 and is maintained for reasons of record and as set forth below.

The teachings of Schooler et al are discussed above and are applied as before.

The teachings of Paweletz et al were discussed above and are applied as before.

Paweletz et al and Schooler et al do not expressly teach the treatment of cells after lysis with a compound, and testing the response of kinase activity within the lysate to a test compound.

Matsui et al teach a method of lysing cells and concentrating a particular kinase activity from the cell lysate. They then provide various cellular proteins as substrates for the kinase activity. They demonstrate that adding a test compound to the kinase changes its activity toward cellular protein substrates; in this case, addition of GTPγS changes the phosphorylation activity of the kinase complex towards its substrates S6 protein, Protein Kinase C, and Myelin Basic Protein (MBP) (see Materials and Methods, p2214-2215, and Fig. 4, p. 2210, as examples).

A person of ordinary skill in the art at the time the invention was made would have been motivated to use the method of Matsui et al of isolating lysate-kinase activity first, and then applying a test compound, in the method of testing phosphorylation equilibrium by binding

phosphoproteins to a solid support, because Matsui et al demonstrate that it is possible to measure a change in phosphorylation status of a substrate by stimulating a kinase activity after cells have already been lysed, and Matsui et al demonstrate that one can concentrate kinase activity and thus have a stronger readout.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to lyse cells before treating them with a compound in a method of studying cell activation.

Response to arguments - 35 USC § 112

Applicants traverse the rejection of claims 1 and 15 in the Office Action mailed 8 January 2007 under 35 USC 112, first paragraph, as failing to comply with the enablement requirement.

Applicants argue that Tassan et al conjecture that K35 and SRB10, both CDK8 homologues, might be negatively regulated by phosphorylation at those sites.

Applicants argue that their own work demonstrates that PKA phosphorylates CDK8, and provide a figure in the affidavit submitted 8 June 2007.

Applicants argue that the NetPhos 2.0 server predicted potential phosphorylation sites at 13 serines, 9 threonines, and 4 tyrosines, as well as 4 potential PKA phosphorylation sites.

Applicants also argue that phospho-specific antibodies could be generated by injection of the peptides corresponding to the consensus PKA sites into rabbits, for example, to generate an antibody response.

Applicants' arguments have been fully considered but are not deemed persuasive.

Tassan et al teach that these proteins might be regulated by phosphorylation, but in the next sentence state that it is possible that they are not at all regulated by phosphorylation (see p. 8875, col. 1). It is also clear from Tassan et al that a function for K35 is not known. Therefore it is impossible for both reasons to determine any state of cell activation from phosphorylation of CDK8.

The experimental data provided by Applicants is also not persuasive. It is well known in the art that in *in vitro* settings, kinases will phosphorylate numerous non-physiological substrates. One example is the use of bovine serum albumin in PKA phosphorylation assays (see Forsyth et al, 1989; p. 138, col. 2, "A-Kinase Activity on Vesicle Protein"; see p. 139, Table 1 and col. 1 text, as examples). Wang and Roach (1993) also teach that it is well known in the practice of kinase assays that in *in vitro* conditions, kinases often phosphorylate targets that they would not phosphorylate in an *in vivo*, physiological setting (see pp. 122-123, for example). Additionally it is almost impossible to see the band Applicants assert is phosphorylated CDK8 in the figure provided, leading one to think the phosphorylation observed is not robust. Lastly Applicants still have not demonstrated how phosphorylation of CDK8, if it occurs in a physiologically relevant manner at all, correlates with any form of cell activation.

The argument that NetPhos can be used to generate phosphospecific antibodies by predicting phosphorylation sites is also unpersuasive. It is well known in the art of kinase signal transduction that software for predicting phosphorylation sites is unreliable. Khan et al (Proteomics, 2005), for example, teach that NetPhos predicted five PKC phosphorylation sites in the orphan nuclear receptor TR2; however only two were actual PKC targets, and only one

changed TR2 transcriptional activity (see Abstract, for example). Therefore, only one of five NetPhos sites showed any measure of changing cellular activity.

All these factors make the argument that Applicants have demonstrated the instantly claimed invention is enabled unpersuasive.

Applicants argue that it is well known in the art that PAK6 phosphorylation is indicative of cellular activation, and refer to two previous references for support at p. 9 of the Remarks dated 8 June 2007.

This argument has been fully considered but is not deemed persuasive.

It is an accepted fact that PAK6 is phosphorylated in cells, and that it can respond to extracellular stimuli. However Applicants have nowhere demonstrated how PAK6 phosphorylation correlates with cell activation, much less in concert with CDK8 or any other protein. Hence Applicants have nowhere demonstrated that the instantly claimed invention is enabled for determining cell activation by measuring PAK6; at best, the references cited in the Remarks submitted 8 June 2007 (at page 9, specifically) demonstrate the instantly claimed invention is anticipated (referring to Lee SR et al, 2002).

Response to arguments - 35 USC § 102

Applicants traverse the rejection of claims 1, 4, 7, 8, 11, 12, and 14 in the Office Action mailed 8 January 2007 under 35 USC 102(b), as being anticipated by Schooler et al (Anal Biochem, 2000). Based on Applicant's amendment, this rejection is withdrawn.

Response to arguments - 35 USC § 103

Applicants traverse the rejection of claims 1, 4, 7-9, 11, 12, 14, 22-27, and 29 in the Office Action mailed 8 January 2007 under 35 USC 103(a), as being unpatentable over Schooler et al (Anal Biochem, 2000) in view of Paweletz et al (Oncogene, 2001).

Applicants argue in their affidavit that there is an unexpected benefit from measuring the phosphorylation state of three proteins instead of two as exemplified by Paweletz et al. Applicants argue that there is an unexpected benefit from measuring three proteins instead of two; for example, were one to measure only c-Jun, one would have the impression that cell activation is not changed. Additionally Applicants argue that by determining the phosphorylation state of three proteins instead of two one of skill in the art can determine specifically which kinase cascades are being activated.

Applicants' arguments have been fully considered but are not deemed persuasive.

It should be noted at the outset that Paweletz et al measured the post-translational modification of four proteins; by chance only two happened to be modified by phosphorylation. If they believed that the activity of all four proteins were changed by phosphorylation, rather than proteolysis for example, it would be clear that the method of Paweletz would be useful for such analysis. Paweletz et al also teach, however, that their assay is *generally* applicable to measuring protein phosphorylation in different cell physiological states. They do not place a limit on how many phosphorylated proteins one may measure. For example, they suggest that GSK3-β is also a phosphorylated protein in the Akt-PI3K pathway; it would be logical to one of ordinary skill in the art to use Paweletz's method to additionally measure changes in GSK3-β phosphorylation (see Discussion, pp. 1986-7, for example).

Schooler also suggests that his method is not limited to simply EGFR, but is applicable to measuring phosphorylation of tyrosine kinases generally in a method of determining a cell activation state (see Discussion, last para col. 1 to first para col. 2, p. 141, for example). The teachings of Paweletz et al and Schooler et al make clear that their assays are meant for general determination of protein phosphorylation and not strictly limited to the examples they describe.

As discussed above, Applicants claim a method of determining cell activation by measuring the phosphorylation state of three proteins instead of two. Applicants have argued that measuring three proteins instead of two allows one to determine which kinase cascade been activated. However Applicants have argued that determining the phosphorylation state of any three proteins from tables 1, 2, and 3 allows such determination. Such an assertion is not logically possible. Furthermore, as a representative selection of three proteins, Applicants have named CDK8, PAK6, and MKK3. There is no evidence that these three proteins have anything to do with each other in terms of signaling cascades, especially considering that it is controversial whether CDK8 is phosphorylated at all, not to mention what the role of any such phosphorylation would be. Applicants have provided no indication as to what unexpected benefit would be gained from measuring the phosphorylation state of MKK3, PAK6 and CDK8.

Conclusion

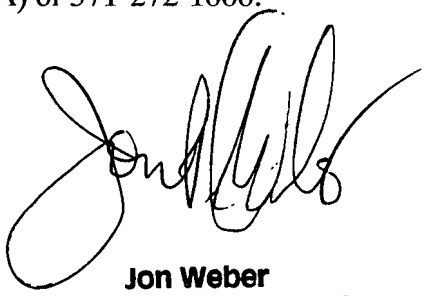
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clark D. Petersen whose telephone number is (571)272-5358. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571)272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CDP 8/2/2007



Jon Weber
Supervisory Patent Examiner